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SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE

SAN FRANCISCO, CALIFORNIA 94143

June 9, 1982

Council for Tobacco Research, Inc.
110 East 59th St.
New York, NY 10022

Dear Sir:

My colleague, John D. Stobo, M.D., and I are writing you in hope of interesting The Council for Tobacco Research in funding a research project in our laboratory. We are investigating immunological and molecular aspects of malignant cells and their transofrmation to more differentiated (functionally competent) cells. Specifically, we have focused on the human monocyte-macrophage-like neoplastic cell line U 937. The markers we are following are the cell surface histocompatibility antigens, HLA-DR, for which we have both immunological and molecular probes.

In the resting stage U-937 appears immature, high anaplastic, and does not display HLA-DR determinants. We can induce these cells to differentiate into functional macrophages which express HLA-DR antigens. Two signals are required for this induction. The first signal is azacytidine, which is known to differentiate fibroblasts and white blood cell precursors in vitro, and which acts by undermethylating DNA thus exposing new genes to transcriptional control. The second signal is provided by a soluble material obtained from activated T cells. Having established the biological behavior of this system, we are now investigating the molecular and immunological mechanisms of this differentiation.

With cDNA probes we are studying the conformational changes occurring in genes coding for HLA-DR determinants, their transcriptional control, and the processing of their transcripts. On the protein level, we have already established that faithful assembly of these proteins occurs. Finally, we have cloned antigen responsive T cells of the same HLA-DR haplotype in order to reconstitute an antigen presentation system in vitro, thus firmly establishing the functionality of the responsive cell line.

The implications of these studies are far reaching and provide an interface between tumor biology, immunology, and molecular genetics. Perhaps you can share our excitement. If so, please indicate whether a more formal research application can be submitted.

Thank you very much for your consideration.

Sincerely yours,.

B. Matija Peterlin, M.D.